

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
14 October 2004 (14.10.2004)

PCT

(10) International Publication Number  
**WO 2004/087681 A1**

- (51) International Patent Classification<sup>7</sup>: **C07D 257/04**, A61K 31/41
- (21) International Application Number: PCT/IN2003/000096
- (22) International Filing Date: 31 March 2003 (31.03.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (71) Applicant (for all designated States except US): **HETERO DRUGS LIMITED** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018, Andhrapradesh (IN).
- (72) Inventors; and  
(75) Inventors/Applicants (for US only): **PARTHASARADHI, Reddy, Bandi** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018, Andhrapradesh (IN). **RATHNAKAR, Reddy, Kura** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN). **RAJI, Reddy, Rapolu** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN). **MURALIDHARA, Reddy, Dasari** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Declarations under Rule 4.17:**  
— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations  
— of inventorship (Rule 4.17(iv)) for US only
- Published:**  
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: A NOVEL AMORPHOUS FORM OF VALSARTAN

(57) Abstract: The present invention relates to a novel amorphous form of valsartan, to a process for its preparation and to a pharmaceutical composition containing it.



WO 2004/087681 A1

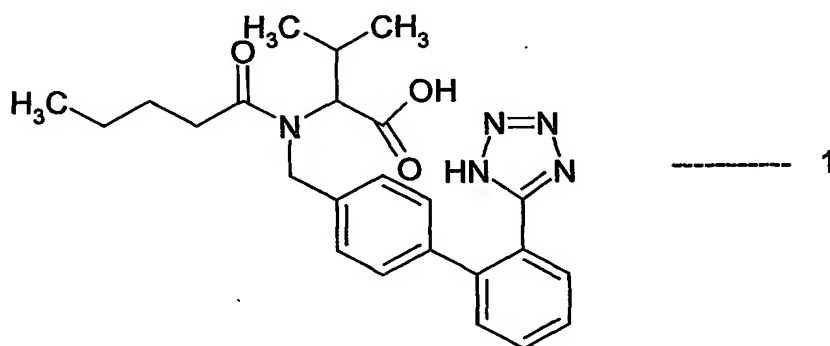
## A NOVEL AMORPHOUS FORM OF VALSARTAN

### FIELD OF THE INVENTION

5       The present invention relates to a novel amorphous form of valsartan, to a process for its preparation and to a pharmaceutical composition containing it.

### BACKGROUND OF THE INVENTION

10      Valsartan of formula (1):



15      or N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine, is an antihypertensive agent and its therapeutic uses are disclosed in US 5,399,578. No polymorphs of valsartan is reported in the literature.

We discovered a sufficiently stable amorphous form of valsartan, which is found to be suitable for pharmaceutical composition.

20      The object of the present invention is to provide a novel stable amorphous form of valsartan, process the preparing it and a pharmaceutical composition containing it.

### DETAILED DESCRIPTION OF THE INVENTION

25      The present invention provides a novel amorphous form of valsartan (hereinafter referred to as amorphous valsartan). The amorphous valsartan is characterized by having broad x-ray diffraction spectrum as in figure 1.

A further aspect of the present invention provides a process for the preparation of amorphous valsartan. Amorphous valsartan is prepared by dissolving valsartan in an alcohol or a mixture of alcohols. The alcohol is selected from the group consisting of methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol. The solvent may be removed from the solution by vacuum drying or spray drying.

A further aspect of the present invention provides a pharmaceutical composition comprising amorphous valsartan and a pharmaceutically acceptable carrier.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction spectrum of amorphous valsartan.

x-Ray powder diffraction spectrum was measured on a Siemens D5000 x-ray powder diffractometer having a copper-K $\alpha$  radiation.

The following examples further illustrate the invention.

#### Example 1

Valsartan (10 gm), (obtained by the process described in example-16 of US 5,399,578) is dissolved in methanol (50 ml). The solution is subjected to vacuum drying at about 40°C for 10 hours to give 9.8 gm of amorphous valsartan.

#### Example 2

Example 1 is repeated by subjecting the solution to spray drying instead of vacuum drying to give amorphous valsartan.

#### Example 3

Valsartan (10 gm), (obtained by the process described in example-16 of US 5,399,578) is dissolved in ethanol (60 ml). The solution is subjected to vacuum drying at about 45°C for 12 hours to give 9.7 gm of amorphous valsartan.

**Example 4**

Example 3 is repeated by subjecting the solution to spray drying instead of vacuum drying to give amorphous valsartan.

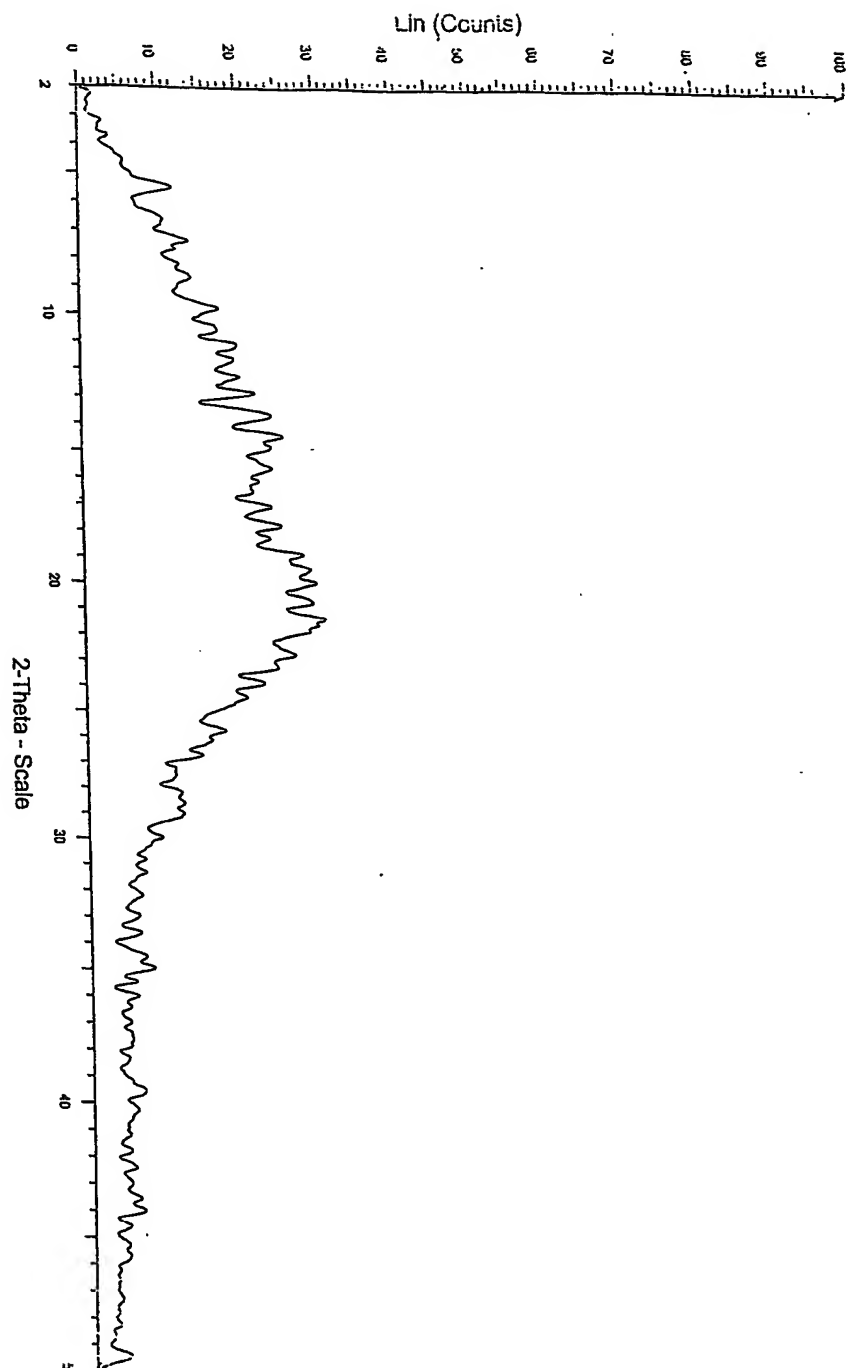
5

**Example 5**

Valsartan (10 gm) is dissolved in isopropyl alcohol (70 ml). The solution is subjected to vacuum drying at about 45°C for 15 hours to give 9.9 gm of amorphous valsartan.

We claim:

1. Amorphous valsartan characterized by an x-ray powder diffraction spectrum as in figure 1.
- 5 2. A process for preparation of amorphous valsartan of claim 1, which comprises:
  - a) dissolving valsartan in an alcohol or a mixture of alcohols;
  - b) removing the solvents from the solution formed in step (a) either by vacuum drying or by spray drying;
- 10 wherein the alcohol is selected from the group consisting of methanol, ethanol isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol.
3. A process according to claim 3, wherein the solvent is removed by vacuum drying.
4. A process according to claim 3, wherein the solvent is removed by spray
- 15 drying.
5. A pharmaceutical composition comprising amorphous valsartan and a pharmaceutically acceptable carrier.



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN 03/00096-0

## CLASSIFICATION OF SUBJECT MATTER

IPC<sup>7</sup>: C07D 257/04, A61K 31/41

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC<sup>7</sup>: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, CAPLUS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5399578 A (Buehlmayer, Peter; Ostermayer, Franz; Schmidlin, Tibur, Ciba-Geigy A.-G.) 21 March 1995 (21.03.95) ; cited in the application. <i>examples 16, 37; claims 1-5; abstract.</i>	1-5
A	WO 2002/006253 A1 (Novartis A.-G.) 24 January 2002 (24.01.02) <i>abstract.</i>	1-5
A	CN 1317485 A (Pharmaceutical Co., Ltd., Changzhou Pharmaceutical Factory No.4, Peop. Rep. China) 17 October 2001 (17.10.01) <i>abstract.</i>	1-5

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

„A“ document defining the general state of the art which is not considered to be of particular relevance

„E“ earlier application or patent but published on or after the international filing date

„L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

„O“ document referring to an oral disclosure, use, exhibition or other means

„P“ document published prior to the international filing date but later than the priority date claimed

„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

„X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

„Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

„&“ document member of the same patent family

Date of the actual completion of the international search

12 August 2003 (12.08.2003)

Date of mailing of the international search report

11 September 2003 (11.09.2003)

Name and mailing address of the ISA/AT

Austrian Patent Office  
Dresdner Straße 87, A-1200 Vienna

Facsimile No. 1/53424/535

Authorized officer

MÜLLER-HIEL R.

Telephone No. 1/53424/434

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN 03/00096-0

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>Jia, Qingzhong; Ma, Guilin; Li, Wenzhi; Jiang, Shaohao            "Synthesis of antihypertensive drug valsartan" Zhongguo Yiyao            Gongye Zazhi (2001), 32(9), 385-387 CODEN: ZYGZEA; ISSN:            1001-8255 (abstract). Chemical Abstracts [online] Copyright            2003 American Chemical Society [retrieved on 12 August 2003            (12.08.03)]. Retrieved from STN International, Karlsruhe.            Chem. Abstr. No. 2001:807594 CAPLUS; abstract.  <i>abstract.</i></p>	1-5



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.  
PCT/IN 03/00096-0

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
CN	A	1317485			none	
US	A	5399578	21-03-1995	AT	E 134624	15-03-1996
				AU	A1 71151/91	22-08-1991
				AU	B2 644844	23-12-1993
				CA	AA 2036427	20-08-1991
				CA	C 2232775	10-06-2003
				CY	A 1978	05-09-1997
				DE	C0 59107440	04-04-1996
				DK	T3 443983	18-03-1996
				EP	A1 443983	28-08-1991
				EP	B1 443983	28-02-1996
				ES	T3 2084801	16-05-1996
				FI	A0 910747	15-02-1991
				FI	A 910747	20-08-1991
				FI	A 980787	06-04-1998
				FI	A0 980787	06-04-1998
				FI	B1 107921	31-10-2001
				GR	T3 3019155	31-05-1996
				HK	A 2199/96	03-01-1997
				HU	A0 910537	30-09-1991
				HU	A2 61271	28-12-1992
				HU	A0 9802895	01-02-1999
				HU	B 219343	28-03-2001
				HU	B 220073	28-10-2001
				IE	A1 910548	28-08-1991
				IE	B 71155	29-01-1997
				IL	A0 97219	25-05-1992
				IL	A1 97219	08-12-1995
				JP	A2 4235149	24-08-1992
				JP	B2 2749458	13-05-1998
				KR	B1 171409	01-02-1999
				LU	A9 90100	25-09-1997
				LU	A9 90362	10-05-1999
				LV	A4 5773	20-12-1996
				LV	B4 5773	20-04-1997
				NO	A0 910630	18-02-1991
				NO	A 910630	20-08-1991
				NO	B1 304023	12-10-1998
				NZ	A 237126	25-11-1994
				PH	A 30484	28-05-1997
				PT	A 96799	31-10-1991
				PT	B 96799	30-09-1998
				US	A 5965592	12-10-1999
				ZA	A 9101179	27-11-1991
WO	A	20020062			none	
		53				